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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,658	01/09/2002	Eric N. Olson	MYOG:024USC1	7444

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,658	OLSON, ERIC N.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 5-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/438,075, filed November 10, 1999, now US Patent 6,372,957, which claims benefit to provisional applications 60/107,755, filed November 10, 1998 and 60/108,083, filed November 12, 1998.

Claims 1-9 are pending.

Election/Restrictions

Applicant's election without traverse of group III, claims 4 and 9, in the reply filed on April 5, 2004, is acknowledged.

Claims 1-9 are pending. Claims 1-3, 5-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 5, 2004. Claims 4 and 9, drawn to a method of treating hypertrophy in a cardiomyoctye comprising the steps of (1) decreasing the expression of MEF2 gene; and (2) further decreasing the expression of a gene that is upregulated by MEF2, are currently under examination.

As noted in the restriction requirement, claim 1 link(s) inventions I-III. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all

the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP ' 804.01.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on March 18, 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Specifically, throughout the specification and on pages 83-95 (an extensive listing of references) references have been cited but not been provided nor listed in an IDS. Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's

attention is directed to the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Specifically, Figure 14A contains sequences that have not been identified by sequence identifiers neither in the figure itself not in the short description of the figures on page 11. In addition, page 76 of the specification recites a sequence containing a MEF2 site used in generating transgenic mice. Additionally, it is noted that a sequence listing, CFR and the appropriate declaration have not been submitted.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The elected invention encompasses a method of treating hypertrophy in a cardiomyoctye comprising the steps of first decreasing the expression of MEF2 gene and further decreasing the expression of a gene that is upregulated by MEF2. The specification teaches that MEF2C is important in vascular development during embryology, and absence of MEF2C in transgenic mice results in embryo death at E9.5 days. Further, an analysis of genes important in vascular development which contain promoters with MEF2 binding sites indicate that MEF2C alone is not important in the regulation of these genes because even in the absence of MEF2C these genes are expressed. Using promoter reporter constructs containing the MEF2 binding site, a correlation between hypertrophy and upregualtion of MEF2 binding/promoter activity is made (example 4). While evidence in the art at the time of filing teaches that cardiac hypertrophy has

been shown to be controlled by a signaling pathway involving calcineurin and the transcription factor NFAT3, alternative pathways could also be involved (page 82). Based on the change of expression of the MEF2 reporter construct and its role in embryological vascular development it is proposed that HDAC and CaMK signaling also may play a role in these processes. However, the art teaches that hypertrophy is a complex process of signal transductionand while MEF2 is activated during hypertrophy, there is no direct link between MEF2 causing the hypertrophy. Importantly, in view of the teaching of the specification and the art of record there are several issues regarding the ability to target MEF2 in treating hypertrophy. First, since multiple pathways exist that end in a hypertrophic state lacking any clear and distinct role for MEF2 in all these pathways (Olson JCI 113:1110-1112, 2004) it would appear that simply inhibiting MEF2 will have no affect. While MEF2 animal models have been important in defining the potential role of MEF2, they have served best to demonstrate that separate and distinct pathways exist that cause hypertrophy (Prassier *et al.* JCI 105(10):1395-1406, 2000). Additionally, it should be noted that MEF represents a family of encoded proteins of which only MEF2C has been implicated in endothelium cell survival, while study of the others have provided no correlation. Second, while the evidence of record does indicate that MEF2 expression/activity goes up in response to signaling cascades associated with hypertrophy, from the evidence of record it is unclear whether decreasing MEF2 once a cell is hypertrophic will result in any affect. For example, even if overexpression of MEF2 was demonstrated to cause the hypertrophic state there is no evidence that reducing or removing the activity of MEF2 will result in treatment by ameliorating the affect on the cell. However as discussed above, it should be noted that even as of 2004 the inventor acknowledges that it is still to be determined whether MEF2 is involved in

the pathogenic mechanisms associated with endothelial disorders (third column, page 1111, Olson JCI 113:1110-1112, 2004). This is complicated even further by the fact that MEF2 alone does not regulate gene expression and as acknowledged by the instant specification these specific partners remain to be defined (page 5, top of page). Finally, the instantly claimed method requires further inhibiting genes upregulated by MEF2 however the instant specification does not identify any of these potential target genes. (page 1404, top of first column, Prassier *et al.* JCI 105(10):1395-1406, 2000). While Examiner would acknowledge that the art teaches that family of MEF2 transcriptional factors regulate the expression of numerous muscle specific and growth factor inducible genes (for example Black *et al.* Ann Rev Cell Dev Bol 14:167-196), neither the art of record nor the instant specification teach which of these one should even begin to target to affect hypertrophy.

The instantly claimed method is based in part on the up-regulation of the MEF2 during hypertrophy and the important role of MEF2C in heart growth and development. However, the instant disclosure fails to provide a clear correlation that decreasing any MEF2 family member will affect hypertrophy. Further, the disclosure fails to provide any specific guidance to what further genes to target for inhibition. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, it is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of

the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). In the instant case, there is evidence that MEF2C plays a role in the signal transduction pathway that is activated during conditions that cause hypertrophy, however there is no nexus between this observation and the direct role of all the family members of MEF2 causing hypertrophy. While the evidence of record supports a role for MEF2 in signal transduction during hypertrophy the specification provides insufficient teaching and guidance that the therapeutic methods of treatment proposed would work.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of treatment constitute such a "germ of an idea" because a direct role of all the MEF2 family members causing hypertrophy has not been established. Further, there is no specific guidance to what further upregulated MEF2 genes should be subject to inhibition and that would result in treatment.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Breitbart RE, London B, Nguyen HT, Satler CA. Ann Thorac Surg. 1995 Dec;60(6 Suppl):S509-12. Recent advances in the Laboratory of Molecular and Cellular Cardiology.

Kolodziejczyk SM, Wang L, Balazsi K, DeRepentigny Y, Kothary R, Megeney LA. Curr Biol. 1999 Oct 21;9(20):1203-6. MEF2 is upregulated during cardiac hypertrophy and is required for normal post-natal growth of the myocardium.

Czubryt MP, Olson EN. Recent Prog Horm Res. 2004;59:105-24. Balancing contractility and energy production: the role of myocyte enhancer factor 2 (MEF2) in cardiac hypertrophy.

Conclusion

No claim is allowed. The linking claim has not been found allowable so the examination has not been extended to the remaining linked inventions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

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